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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILLIAMS, LEONARD M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,935	DUMAS, JACQUES	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-24,26 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-24, 26 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Response to Arguments

Applicant's arguments filed 3/27/2006 have been fully considered but they are not persuasive. The applicant's state on page 1 of the reply that the only outstanding rejection alleges a lack of enablement for the treatment of rheumatoid arthritis with the compounds recited in the claims. The examiner respectfully disagrees. While the lack of enablement for the treatment of rheumatoid arthritis with the compounds recited in the claims is one aspect of the lack of enablement rejection, it is by no means the only issue addressed in the enablement rejection of record. Specifically the examiner has set forth on page 3 of the office action that the breadth of the claims greatly exacerbates the nature of the invention in that up to 100 million different compound embodiments are encompassed. Further the guidance of the specification discloses 38 of the possible 100 million compounds in Table 1 (pages 40-44 of the specification).

In order to clarify, the examiner respectfully points out that Table 1 includes structural data, mass spectral data, TLC data, TLC solvent system data, melting point data and synthetic means data. There is no mention of activity data for any of the compounds in Table 1. Further the examiner points out that the two assays performed are an *in vitro* p38 inhibition assay and a LPS induced TNFa production mouse assay. Neither of these assays are specific for rheumatoid arthritis.

The examiner respectfully points out that in the *in vitro* p38 inhibition assay the applicant's state:

"The *in vitro* inhibitory properties of compounds were determined using a p38 kinase inhibition assay."

and later

"All compounds exemplified displayed p38 $IC_{50's}$ of between 1 nM and 10 μM."

The applicant's referral to "all compounds exemplified" does not clearly limit what compounds were tested (all compounds exemplified in the specification or only compounds exemplified in Table 1, etc...). Further the assertion that the compounds exhibited IC_{50s} of from 1nM to 10 μM does not guide one as to what compounds have activity and as the difference in activity of from 1nM to 10 μM is more than a 1000 fold one would need to know the activity profile of the specific compounds tested in order to understand the scope and breadth of the invention.

The issue is furthered muddled by the LPS induced TNFα production mouse assay as the applicant's state:

"The *in vivo* inhibitory properties of selected compounds were determined using a murine LPS induced TNFα production *in vivo* model."

The applicants do not disclose which "selected compounds" were tested and do not disclose the activity of the "selected compounds".

The examiner respectfully points out that the applicant's did not test the compounds in accepted specific rheumatoid arthritis assays.

In summary the applicants have not specifically described the compounds tested in the p38 assay or LPS induced TNFα production mouse model, they have not correlated the structure of the compounds tested with their relative activity in said assays and they have not tested the compounds in a specific rheumatoid arthritis assay. It is for these reasons and for the reasons of record that the 112-1 enablement rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-24, 26 and 30-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 09/947761. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 17 of the current application is drawn to a method for the treatment of rheumatoid arthritis which

comprises administering a compound of formula I wherein formula I is an urea with functionalities A and B. Claim 1 of the '761 application is drawn to a method for treatment of a diseases, other than cancer, mediated by p38, comprising administering a pharmaceutical composition comprising a compound of formula I wherein formula I is an urea with functionalities A and B. Both the current claims and the '761 application claims define A and B as having equivalent scope and breadth. Further claim 1 of '761 is a broader claim than current claim 17.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-19, 22, 26 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention

is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***The Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to the treatment of rheumatoid arthritis with a heterocyclic substituted urea.

(2). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a treatment comprising the administration *any* urea encompassed by the formula illustrated by the broad generic structure of formula I. The nature of the invention is complex in that it potentially encompasses a vast number of compounds. For example, when B is phenyl, X is an amide and A is a diazole, R5 and R5' can be independently selected from more than 43 groups; R1 can be selected from 34 groups; and R1' can be selected from 16 groups (which may, in turn, be substituted with more than 100 different groups in various

numbers and patterns). A basic look at a single variable of what A, B and Xn (when n is 1) may be leads to variations numbering in excess of (43x43x34x16x100) 100 million possibilities. It is noted that A may be selected from at least 26 groups; B is selected from 3 groups; n is 0-3; and X is selected from at least 88 different groups (many of which may be substituted with the at least 43 groups of R5 and R5').

(3). ***Guidance of the Specification***:

The guidance given by the specification as to what types of ureas would be useful in a method of the instant invention is limited. Applicant discloses 38 different ureas as ureas useful in *inhibiting p38*. The specification does not teach that the scope of the invention is limited to these ureas and the claims do not claim a method of inhibiting p38, however.

(4). ***Working Examples***:

As discussed above, the working examples show 38 compounds that are capable of inhibiting p38. None are shown to be actually effective at treating rheumatoid arthritis.

(5). ***State of the Art***:

Applicant's assessment of the prior art indicates that inhibition p38 has been shown to inhibit cytokine production (e.g. TNFα, IL-1, IL-6, IL-8) and that TNFα has been linked to rheumatoid arthritis. There is no indication that inhibition of p38

invariably inhibits each of the cytokines listed (as each are simply examples), nor is there any indication that the inhibition of p38 would invariably lead to the treatment of rheumatoid arthritis. Even if we were to assume that an inhibition of p38 would lead to the desired inhibition of TNFα, a link between TNFα production and rheumatoid arthritis doesn't mean that any inhibition of TNFα would treat the rheumatoid arthritis. It is further noted that the specification likewise indicates that TNFα production is linked to numerous other diseases (see pages 2-5 of the specification).

(6). ***Predictability of the Art***:

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, as discussed above, there is a vast number of compounds encompassed by the claims wherein only 38 of them have been shown to be effective at inhibiting p38. Furthermore, there is no evidence that the compounds actually treat rheumatoid arthritis; it is simply postulated that because these compounds inhibit p38 that they will in turn inhibit TNF□ and that they will in turn treat rheumatoid arthritis.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compound represented by formula I. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th

ed., 1996), page 51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharaceutical compositions herein. Thus, the teachings of *Goodman & Gilman* clearly support that the instant claimed invention is highly unpredictable.

(7). ***The Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of the broad use of any compound represented by formula I. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention. Furthermore, one of skill in the art would have to determine not only which compounds inhibit p38, but which compounds actually treat rheumatoid arthritis.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Conclusion

This action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER